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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: DI SALLE Enrico et al.
SERIAL NO.: NEW U.S. PCT APPLICATION
FILED: HEREWITH
INTERNATIONAL APPLICATION NO.: PCT/EP00/03407
INTERNATIONAL FILING DATE: April 14, 2000
FOR: COMBINED METHOD OF TREATMENT COMPRISING AN AROMATASE INHIBITOR AND A FURTHER BIOLOGICALLY ACTIVE COMPOUND

REQUEST FOR PRIORITY UNDER 35 U.S.C. 119 AND THE INTERNATIONAL CONVENTION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In the matter of the above-identified application for patent, notice is hereby given that the applicant claims as priority:

COUNTRY	APPLICATION NO	DAY/MONTH/YEAR
Great Britain	9911582.6	18 May 1999

Certified copies of the corresponding Convention application(s) were submitted to the International Bureau in PCT Application No. PCT/EP00/03407. Receipt of the certified copy(s) by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

Respectfully submitted,
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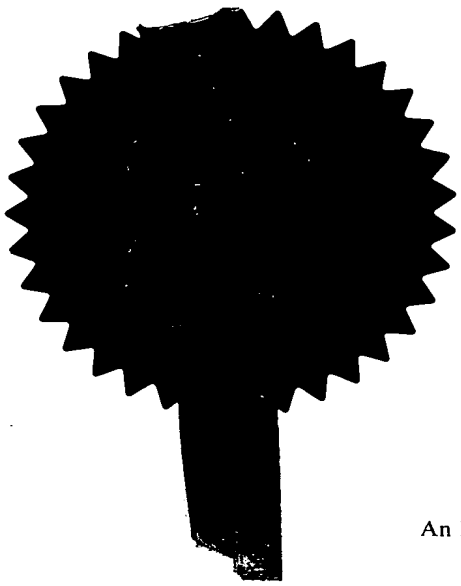

Signed Andrew Gersey

Dated 9 February 2000

Patents Form 7/77

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The Patent Office

Statement of inventorship and of right to grant of a patent

The Patent Office

Cardiff Road
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1. Your reference	P.76977 GCW.CMK
2. Patent application number *(If you know it)*	9911582.6
3. Full name of the or of each applicant	.PHARMACIA & UPJOHN S.P.A.
4. Title of the invention	COMBINED METHOD OF TREATMENT COMPRISING AN AROMATASE INHIBITOR AND A FURTHER BIOLOGICALLY ACTIVE COMPOUND
5. State how the applicant*(s)* derived the right from the inventor*(s)* to be granted a patent	As employer
6. How many, if any, additional Patents Forms 7/77 are attached to this form? *(see note (c))*	
7.	I/We believe that the person*(s)* named over the page *(and on any extra copies of this form)* is/are the inventor*(s)* of the invention which the above patent application relates to. Signature JA Kemp Date 18 May 1999
8. Name and daytime telephone number of person to contact in the United Kingdom	Mrs C M Keen 0171 405 3292

THE PATENT OFFICE
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18 MAY 1999
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Enter the full names, addresses and postcodes of the inventors in the boxes and underline the surnames

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Request for grant of a patent

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18 MAY 1999

The Patent Office

Cardiff Road
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1. Your reference — P.76977 GCW.CMK

2. Patent application number *(The Patent Office will fill in this part)* — **9911582.6**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — PHARMACIA & UPJOHN S.P.A.

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Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — Italy

4. Title of the invention — COMBINED METHOD OF TREATMENT COMPRISING AN AROMATASE INHIBITOR AND A FURTHER BIOLOGICALLY ACTIVE COMPOUND.

5. Name of your agent *(if you have one)* — J A KEMP & CO

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6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body:
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Patents Form 1/77

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Continuation sheets of this form	
Description	13
Claim(s)	6
Abstract	1
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Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	1 x 4
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature JA Kemp & Co Date 18 May 1999

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs C M Keen
0171 405 3292

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(FC 859)

Combined method of treatment comprising an aromatase inhibitor and a further biologically active compound.

Field of the invention

The present invention relates to a method of treatment of human breast cancer and in particular to combination therapy involving administration of an aromatase (estrogen synthetase) inhibitor in combination with mono-or-polichemotherapy with cytotoxic agents.

Background of the invention

Since 1896 it has been demonstrated by Cecil Beatson that ovariectomy resulted in tumor regression in premenopausal breast cancer patients. Subsequently, estrogens were identified as the mediator of ovarian dependency. The biological effect of estrogens was found to be mediated by the stimulation of a nuclear estrogen receptor (ER), which belong to a family of hormone-activated transcription factors that can initiate or enhance the transcription of genes containing specific hormone response elements. Further, the sensitivity of breast cancer to estrogens has been found to increase in tumors positive for ER.

Over the last two decades, several approaches have been attempted to develop pharmacological agents able to reduce estrogen effect. Two pharmacological approaches are currently available:

1) the antiestrogens, which antagonize the effect of estrogens at the ER level;

2) the aromatase (estrogen synthetase) inhibitors, which inhibit the estrogen production, i.e., the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively.

The prototype antiestrogen, tamoxifen, is now largely used in the adjuvant systemic therapy of localized breast cancer (i.e., systemic therapy given at the time of primary local treatment in the absence of demonstrated metastasis) and in the treatment of the advanced

(metastatic) breast cancer. However, resistance to tamoxifen occurs, due to: 1) the intrinsic estrogenic effect of tamoxifen (i.e., partial estrogen agonism); 2) the formation of tamoxifen's estrogenic metabolites; 3) the stimulation by tamoxifen and its metabolites of a mutated ER; 4) the growth of estrogen independent tumor cells. In addition, some concerns are now being considered in the use of tamoxifen in the early disease, due to the increased risk of endometrial cancer.

Therefore, new hormonal therapies without the negative effects of either tamoxifen or other similar compounds are under extensive evaluation.

One of such new antihormonal treatment modality of breast cancer is represented by the aromatase inhibitors. In the premenopausal women the ovarian aromatase is the main source of circulating estrogens. In the postmenopausal women adipose tissue is considered to be the main site for estrogen synthesis. In addition, aromatase activity has been shown in the breast tissue, including the tumor itself. Therefore, the very high levels of intratumoral estrogens in comparison to the circulating estrogens are due to the local estrogen synthesis through the aromatase enzyme.

Various steroidal and non-steroidal compounds have been described as aromatase inhibitors, including the steroidal derivatives exemestane and formestane, and the non-steroidal derivatives aminoglutethimide, vorozole, fadrozole, letrozole, anastrozole and YM511 (K.M. Susaki et al. J. Steroid. Biochem. Molec. Biol. 58, 189-194, 1996).

Many clinical trials have shown that these compounds represent an effective second-line treatment for metastatic breast cancer refractory to tamoxifen.

In addition, these compounds are being clinically evaluated in the adjuvant setting, either alone or combined with tamoxifen, and as first-line treatment of the metastatic disease.

The more complete estrogen blockade via aromatase inhibition is expected to result in greater tumor response than with tamoxifen, due to the weak or partial estrogen agonist effect of tamoxifen as above discussed.

Breast cancer was one of the first solid tumor to be treated with chemotherapy with cytotoxic agents, and one of the first tumors to be treated with polychemotherapy. Menopausal status and ER status play important role in therapy selection either in early or metastatic breast cancer. Chemotherapy is more commonly used in premenopausal women

which are more likely to have ER-negative tumors. In the advanced disease, chemotherapy is recommended in the ER-negative tumors and after hormonotherapy failures in the ER-positive tumors. In several randomized trials, polychemotherapy has been established to the superior to monochemoterapy either in the adjuvant or metastatic setting.

The cytotoxic compounds generally used in the polychemotherapy of breast cancer or under clinical evaluation belong to various classes including:

1) Topoisomerase II inhibitors, such as the antracyclines doxorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide.
2) Antimicrotubule agents, such as the taxanes paclitaxel and docetaxel, and the vinka alkaloids vinblastine and vinorelbine.
3) Alkylating agents, such as cyclophosphamide, ifosfamide and melphalan and the alkycycline derivative PNU-159548 (C. Geroni et al., Proc. Am. Assoc. Cancer Res 39, p223, 1998 (Abstr. #1517).
4) Antineoplastic antimetabolites, such as 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate.
5) Topoisomerase I inhibitors, such as topotecan, irinotecan, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO99/17804).

Despite intensive efforts directed at prevention and early diagnosis, breast cancer remains one of the leading causes of morbidity and mortality in women. Although early-stage disease is now frequently cured by surgical intervention and adjuvant hormonal and/or chemotherapy, the prognosis for women with advanced or with metastatic disease remains poor. In fact, a median survival of only 2-3 years has been consistently reported over the last 20 years, in spite of the introduction of novel agents. Therefore, in advanced breast cancer patients, palliation of symptoms remains one of the primary objectives of treatment, and maintaining a reasonable quality of life is of paramount importance. Hormonal therapy is often the treatment of choice in such patients. However, currently hormonal treatments of breast cancer cause, in patients not selected on the basis of their receptor status, only a

maximal response rate of 30-35%. The median duration of response is 1 to 2 years and is influenced by the site of disease. If a patient's cancer responds to hormonal therapy but later progressed, the cancer may respond again to a second hormonal therapy, but the response rate decreases and the duration of response become shorter. Eventually, nearly all breast cancers become refractory to hormonal manipulation and the patients are candidates for cytotoxic chemotherapy. Chemotherapy is more toxic than hormonal therapy, therefore is in general reserved for patients refractory to hormonal treatment or in patients with extensive visceral involvement, or if the tumor is growing rapidly. Combination chemotherapy is generally more effective than single agent treatment. However, only 15% of patients have a complete remission, the duration of the response is limited, all the tumors become resistant to chemotherapy and the patients die.

Therefore a major goal in breast cancer therapy is to develop new treatment modalities in order to increase tumor response and survival.

Accordingly, it would be desirable to have a drug combination modality having improved action than currently used treatment modalities. Ideally such combination should have increased efficacy, e.g. by providing both a better controlling of breast tumor growth and a longer duration of action, while resulting in less toxic side-effects, thus allowing administration of lower dosage levels of chemotherapeutic agent.

After an extensive study the present inventor has surprisingly found that the therapeutic effect of a chemotherapeutic cytotoxic (antineoplastic) agent is significantly improved and side-effects decreased by co-administering it with an aromatase inhibitor antitumor agent, i.e. a compound which inhibits the formation of estrogens by inhibiting the enzyme aromatase.

Description of the invention

In a first aspect, the present invention provides the use of an antineoplastic agent in the manufacture of a pharmaceutical composition for treatment of breast cancer, the treatment additionally comprising administration of at least one pharmaceutical composition comprising an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect.

The present invention also provides a product containing (a) an antineoplastic agent and (b) an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, as a combined preparation for simultaneous, separate or sequential use in breast cancer therapy in humans.

The present invention also provides a composition of matter for use in breast cancer therapy in humans, comprising (a) an antineoplastic agent in a pharmaceutically acceptable carrier and/or diluent, and (b) an aromatase inhibitor in a pharmaceutically acceptable carrier and/or diluent, in amounts effective to produce a superadditive antitumor effect.

A further aspect of the present invention is a breast cancer therapy method for use in humans, in need thereof, the method comprising administering to said human (a) an antineoplastic agent and (b) an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect.

The invention also provides a method for lowering the side effects caused by breast cancer therapy with an antineoplastic agent in humans, in need thereof, the method comprising administering to said mammal a combination preparation of (a) an antineoplastic agent and (b) an aromatase inhibitor, in a quantity to produce a superadditive antitumor effect.

Accordingly, said combination preparation can be used for lowering the side-effects caused by breast cancer antineoplastic therapy in mammals, including humans, while controlling the growth of neoplasm formation.

According to a preferred aspect of the present invention the superadditive antitumor effect results in an anti breast cancer therapy having increased effectiveness in controlling, i.e. slowing, interrupting, arresting, stopping or reversing, the neoplasm formation.

According to the present invention as "superadditive effect" is meant an effect in controlling the growth of the neoplasm, which is greater than the sum of the actions of the individual components. As used herein, "controlling the growth" of the neoplasm refers to slowing, interrupting, arresting or stopping its growth and it does not necessarily indicate a total elimination of the neoplasm.

The term "antineoplastic agent" is meant to comprise both a single antineoplastic cytotoxic drug and "cocktails", i.e. mixtures of such drugs, according to the clinical practice.

In the combined preparations, pharmaceutical compositions and methods of treating, according to the present invention, the antineoplastic agent may comprise 1 to 4, preferably 1, 2 or 3, antineoplastic drugs, in particular a single antineoplastic drug.

The term "aromatase inhibitor" is meant to comprise both a single aromatase inhibitor agent and cocktails of such inhibitors.

In the combined preparations, pharmaceutical compositions and methods of treating, according to the present invention, the aromatase inhibitor preferably comprises 1 or a mixture of 2 aromatase inhibitor agents, in particular a single aromatase inhibitor agent.

The combination preparation according to the invention can also include combination packs or compositions in which the constituents are placed side by side and can therefore be administered simultaneously, separately or sequentially to one and the same human being.

An antineoplastic agent, according to the invention, is preferably selected from the group comprising: an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite and an antineoplastic topoisomerase I inhibitor.

An antineoplastic topoisomerase II inhibitor is preferably:

a) an anthracycline compound e.g. doxorubicin (including liposomal formulations), epirubicin (including liposomal formulation), idarubicin and nemorubicin; and

b) an anthraquinone compound e.g. mitoxantrone and losoxantrone; and

c) a podophillotoxine compound e.g. etoposide and teniposide.

An antimicrotubule agent is preferably:

a) a taxane compound e.g. paclitaxel (including liposomal formulations) and docetaxel; and

b) a vinca alkaloid e.g. vinblastine and vinorelbine.

An alkylating agent is preferably cyclophosphamide, ifosfamide, melphalan and PNU 159548.

An antineoplastic antimetabolite agent is e.g. 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate.

An antineoplastic topoisomerase I inhibitor is e.g. topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

An antineoplastic agent is preferably epirubicin, doxorubicin, liposome-encapsulated doxorubicin, docetaxel, paclitaxel and liposome-encapsulated paclitaxel.

An aromatase inhibitor according to the present invention may be a steroidal compound, in particular a steroidal compound selected from exemestane and formestane, or a non-steroidal compound selected from aminoglutethimide, fadrozole, vorozole, letrozole, anastrozole and YM 511.

Preferably an aromatase inhibitor is a compound selected from exemestane, anastrozole, fadrozole or letrozole, in particular exemestane.

Particularly preferred preparations, pharmaceutical compositions and methods of treating, according to the present invention, are those comprising a) 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and b) one or two, in particular one, steroidal aromatase inhibitor selected from exemestane, formestane, anastrozole, letrozole and fadrozole.

More preferably are those comprising a) one or two, in particular one, antineoplastic agent selected from epirubicin and docetaxel and b) exemestane.

Pharmacology

As stated above the present inventor has discovered that using a combination of an aromatase inhibitor and a cytotoxic agent it is possible to obtain a better control of the growth of breast tumor growth and a longer duration of tumor response.

The effect of the combination of the present invention is shown for instance by the following *in vivo* experiments which are intended to illustrate but not to limit the present invention.

Antitumor activity in dimethylbenzanthracene (DMBA)-induced mammary tumors in rats

Mammary tumors were induced by a single p.o. administration of 20 mg DMBA in 1 ml sesame oil. Tumors appeared starting about 40 days after DMBA administration. Rats

were selected and placed sequentially into experimental group when at least 1 tumor of 1 cm of diameter was found. The two perpendicular tumor axes were measured with calipers once a week during the experiment. Tumor weight was calculated according to the formula $d^2xD/2$ where d is the minimal and D the maximal diameter.

Tumor growth of control and treated groups were expressed as ratio of initial tumor weight, measured the first day of treatment. At the end of the treatment period (week 4) tumor response to the drug was designed as CR (complete remission, disappearance of the tumor), PR (partial remission, >50% reduction in tumor weight); NC (no change, ≤50% increase or decrease) or P (progression, >50% increase). In addition, the appearance of new tumors during the 4-week treatment regimen was evaluated.

Exemestane, dissolved in benzylic alcohol (3% of final volume) and diluted in sesame oil, was administered s.c., 6 days a week for 4 weeks. Epirubicin, dissolved in sterile 0.9% NaCl solution, was administered i.v., once a week for 4 weeks. Docetaxel, dissolved in 13% ethanol and diluted in 5% glucose solution, was administered i.v., once a week for 4 weeks.

Table 1. Effect of 4-week treatment with exemestane alone or combined with epirubicin on DMBA-induced mammary tumors in rats

Exemestane mg/kg/day s.c.	Epirubicin mg/kg/wk i.v.	No. of rats	No. of tumors	Tumor response (%)					No. of new tumors /rat	Body weight gain (g/4wks
				CR	PR	CR+PR	NC	P		
Control		14	27	0	7	7	26	67	2.1	10
-	1	13	28	0	7	7	36	57	2.1	8
-	3	14	26	12	15	27	27	46	0.5	3
20	-	12	25	20	24	44	20	36	0.6	45
20	1	12	24	42	33	75	17	8	0.7	41
20	3	12	29	48	41	90	10	0	0.0	21

Results in Table 1 indicate that epirubicin was not effective (at 1 mg/kg/day, 7% CR+PR) or less effective (at 3 mg/kg/wk; 27% CR+PR) than exemestane (44% CR+PR) in inducing tumor regressions. When the two drugs were given in combination, a very interesting superadditive antitumor effect was observed in the combination of exemestane

either with the low (75% CR+PR) or the high epirubicin dose (90% CR+PR). The appearance of new tumors was reduced by single treatment with epirubicin 3 mg/kg/wk and exemestane (alone or combined with epirubicin 1 mg/kg/wk). Again, very interestingly the combination of exemestane with epirubicin 3 mg/kg/wk totally prevented the appearance of new tumors during the 4-week of treatment period (2.1 tumors per rat in the control group, versus 0 tumor per rat in the group treated with the combination). Body weight gain indicated that epirubicin, at the tested doses, had a slight inhibitory effect while exemestane showed an anabolizing effect either alone or given in combination.

Figure 1 in particular shows the effect of exemestane and epirubicin given alone or in combination on the growth of DMBA-induced tumors in rats, in which:

—✕— **Control**
—○— **EPI 1 mg/kg/wk**
—●— **EPI 3 mg/kg/wk**
—▲— **EXE 20 mg/kg/day**
- ◻ - **EXE + EPI 1**
- ■ - **EXE + EPI 3**

Figure1 illustrates tumor growth (expressed as ratio of initial tumor weight) during the 4-week treatment period of control and treated groups. The single treatment with exemestane or epirubicin 3 mg/kg/wk caused a reduction of tumor growth, however a higher antitumor effect was observed when the two drugs were combined. Interestingly combined treatments resulted in a longer duration of tumor response: in fact 4 weeks after the end of the treatment (week 8) tumor regrowth was completed in the groups treated with single agents while in the group treated with the combination of exemestane and epirubicin 3 mg/kg/wk tumor weight was still inhibited.

Table 2. Effect of 4-week treatment with exemestane alone or combined with docetaxel on DMBA-induced mammary tumors in rats

Exemestane mg/kg/day s.c.	Docetaxel mg/kg/wk i.v.	No. of rats	No. of Tumors	Tumor response (%) CR	PR	CR+PR	NC	P	No. of new tumor /rat	Body weight gain (g/4wks)
Control		14	27	0	7	7	26	67	2.1	10
-	1.5	13	29	17	24	41	28	31	0.4	0
20	-	12	25	20	24	44	20	36	0.6	45
20	1.5	12	24	75	17	92	4	4	0.0	28

Table 2 shows the results obtained combining exemestane and docetaxel. Docetaxel at 1.5 mg/kg/wk was effective inducing 41% tumor response (CR+PR), an effect similar to that observed after exemestane treatment (44% tumor response). When the two drugs were combined a super additive effect was observed, and almost all tumor regressed (92%). Also the appearance of new tumors was completely suppressed (0 tumor per rat) only with the combination.

It is of note that no obvious increased general toxicity was ever observed with the combinations, as evaluated for instance in terms of body weight loss.

Figure 2 shows the time-course effect of 4-week treatment with exemestane alone or combined with docetaxel on DMBA-induced mammary tumors in rats, in which:

—✕— Control
—○— DOCE 1.5 mg/kg/wk
—●— EXE 20 mg/kg/day
—▲— EXE + DOCE 1.5

As illustrated in Figure 2, the effect of the combination of exemestane and docetaxel was higher than that of single agent and tumor remissions lasted for longer time.

These results support the utilization of an antineoplastic agent in therapy in combination with an aromatase inhibitor antitumor agent.

As used herein, the term "effective antineoplastic amount" refers to an amount which is effective, upon single or multiple dose administration to the patient, in controlling the

growth of the neoplasm or in prolonging the survivability of the patient beyond that expected in the absence of such treatment. As used herein, "controlling the growth" of the neoplasm refers to slowing, interrupting, arresting or stopping its growth and it does not necessarily indicates a total elimination of the neoplasm.

An effective amount of an aromatase inhibitor antitumor agent may vary from about 0.5 to about 500 mg pro dose 1-2 times a day. Exemestane, for example, may be administered orally in a dosage range varying from about 5 to about 50 mg, and particularly, from about 10 to about 25 mg, or parenterally from about 50 to about 500 mg, in particular from about 100 to about 250 mg.

Fadrozole, for example, may be administered orally in a dosage range varying from about 0.5 to about 10 mg, and particularly, from about 1 to about 2 mg.

Letrozole, for example, may be administered orally in a dosage range varying from about 0.5 to about 5 mg, and particularly, from about 1 to about 2.5 mg.

Anastrozole, for example, may be administered orally in a dosage range varying from about 0.5 to about 5 mg, and particularly, from about 1 to about 2 mg.

The effective antineoplastic amounts of the various antineoplastic agents are well known and appreciated in the art.

For example, an effective antineoplastic amount of vinblastine may vary from about 3 mg/m^2 to about 10 mg/m^2.

An effective antineoplastic amount of doxorubicin may vary from about 20 mg/m^2 to about 100 mg/m^2.

An effective antineoplastic amount of epirubicin may vary from about 20 mg/m^2 to about 200 mg/m^2.

An effective antineoplastic amount of idarubicin may vary from about 1 mg/m^2 to about 50 mg/m^2.

An effective antineoplastic amount of mitoantrone may vary from about 10mg/m^2 to about 20 mg/m^2.

An effective antineoplastic amount of paclitaxel may vary from about 100 mg/m^2 to about 300 mg/m^2.

An effective antineoplastic amount of docetaxel may vary from about 50 mg/m^2 to about

100 mg/m^2.

An effective antineoplastic amount of vinorelbine may vary from about 15 mg/m^2 to about 30 mg/m^2.

An effective antineoplastic amount of cyclophosphamide may vary from about 100 mg/m^2 to about 1500 mg/m^2.

An effective antineoplastic amount of melphalan may vary from about 1 mg/m^2 to about 10 mg/m^2.

An effective antineoplastic amount of 5-fluorouracil may vary from about 100 mg/m^2 to about 1000 mg/m^2.

An effective antineoplastic amount of capecitabine may vary from about 10 mg/m^2 to about 1000 mg/m^2.

An effective antineoplastic amount of methotrexate may vary from about 10 mg/m^2 to about 1000 mg/m^2.

An effective antineoplastic amount of topotecan may vary from about 1 mg/m^2 to about 5 mg/m^2.

An effective antineoplastic amount of irinotecan may vary from about 50 mg/m^2 to about 350 mg/m^2.

In effecting treatment of a patient afflicted with a disease state described above an aromatase inhibitor can be administered in any form or mode which makes the compound bioavailable in effective amounts, including oral and parenteral routes. For example, it can be administered orally, subcutaneously, intraperitoneally, intramuscularly, intravenously, transdermally, and the like. Oral or intramuscular administration is generally preferred. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular circumstances, including the disease state to be treated, the stage of the disease, the form of administration of the selected cytotoxic agent and the manner of co-administration selected.

For example, GB-2,177,700 discloses the preparation of pharmaceutical compositions comprising exemestane and a suitable carrier or excipient.

The selected antineoplastic agent can be administered by the appropriate route and dosing schedule as is well known and accepted for the particular agent. For example, epirubicin,

doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinblastine can be administered intravenously. Idarubicin and cyclophosphamide can also be given orally.

Claims

1. A composition for use in breast cancer therapy in humans comprising, in amounts effective to produce a superadditive antitumour effect, (a) an antineoplastic agent in a pharmaceutically acceptable carrier and/or diluent; and (b) an aromatase inhibitor in a pharmaceutically acceptable carrier and/or diluent.

2. A composition according to claim 1, wherein the antineoplastic agent is selected from an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from exemestane, formestane, aminoglutethimide, fadrozole, vorozole, letrozole, anastrozole and YM 511.

3. A composition according to claim 2, wherein the antineoplastic agent is selected from an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.

4. A composition according to claim 3, wherein the anthracycline compound is selected from doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from mitoxantrone and losoxantrone; the podophillotoxine compound is selected from etoposide and teniposide; the taxane compound is selected from paclitaxel and docetaxel; the vinca alkaloid is selected from vinblastine and vinorelbine; the alkylating agent is selected from cyclophosphamide, ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate; and the antineoplastic topoisomerase I inhibitor is selected from topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

5. A composition according to claim 3, wherein such a composition comprises 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and 1 or 2 steroidal aromatase inhibitors selected from exemestane, formestane, anastrozole, letrozole and fadrozole.

6. A composition according to claim 5, wherein the composition comprises one or two antineoplastic agents selected from epirubicin and docetaxel and the steroidal aromatase inhibitor is exemestane.

7. A composition, according to anyone of the preceding claims, wherein:

- the effective antineoplastic amount of vinblastine is from about 3 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of doxorubicin is from about 20 mg/m^2 to about 100 mg/m^2;
- the effective antineoplastic amount of epirubicin is from about 20 mg/m^2 to about 200 mg/m^2;
- the effective antineoplastic amount of idarubicin is from about 1 mg/m^2 to about 50 mg/m^2;
- the effective antineoplastic amount of mitoantrone is from about 10mg/m^2 to about 20 mg/m^2;
- the effective antineoplastic amount of paclitaxel is from about 100 mg/m^2 to about 300 mg/m^2;
- the effective antineoplastic amount of docetaxel is from about 50 mg/m^2 to about 100 mg/m^2;
- the effective antineoplastic amount of vinorelbine is from about 15 mg/m^2 to about 30 mg/m^2;
- the effective antineoplastic amount of cyclophosphamide is from about 100 mg/m^2 to about 1500 mg/m^2;

- the effective antineoplastic amount of melphalan is from about 1 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of 5-fluorouracil is from about 100 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of capecitabine is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of methotrexate is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of topotecan is from about 1 mg/m^2 to about 5 mg/m^2;
- the effective antineoplastic amount of irinotecan is from about 50 mg/m^2 to about 350 mg/m^2;

and the effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.

8. A composition according to claim 7, wherein the amount of aromatase inhibitor exemestane is from about 5 to about 50 mg, fadrozole from about 0.5 to about 10 mg, letrozole from about 0.5 to about 5 mg, and anastrozole from about 0.5 to about 5 mg.

9. Products containing an antineoplastic agent and an aromatase inhibitor for separate, simultaneous or sequential administration in breast cancer therapy in humans.

10. Use of an antineoplastic agent in the manufacture of a pharmaceutical composition for the treatment of breast cancer in a method additionally comprising the administration of an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect.

11. A method for treating breast cancer in humans, the method comprising administering to a human in need thereof (a) an antineoplastic agent and (b) an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect.

12. A method, according to claim 11, wherein the antineoplastic agent is selected from an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from exemestane, formestane, aminoglutethimide, fadrozole, vorozole, letrozole, anastrozole and YM 511.

13. A method according to claim 12, wherein the antineoplastic agent is selected from an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.

14. A method according to claim 13, wherein the anthracycline compound is selected from doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from mitoxantrone and losoxantrone; the podophillotoxine compound is selected from etoposide and teniposide; the taxane compound is selected from paclitaxel and docetaxel; the vinca alkaloid is selected from vinblastine and vinorelbine; the alkylating agent is selected from cyclophosphamide, ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate; and the antineoplastic topoisomerase I inhibitor is selected from topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

15. A method according to claim 13, wherein 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and 1 or 2 steroidal aromatase inhibitors selected from exemestane, formestane, anastrozole, letrozole and fadrozole are administered.

16. A method according to claim 14, wherein one or two antineoplastic agents selected from epirubicin and docetaxel and the steroidal aromatase inhibitor exemestane are administered.

17. A method according to claim 16, wherein:

- the effective antineoplastic amount of vinblastine is from about 3 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of doxorubicin is from about 20 mg/m^2 to about 100 mg/m^2;
- the effective antineoplastic amount of epirubicin is from about 20 mg/m^2 to about 200 mg/m^2;
- the effective antineoplastic amount of idarubicin is from about 1 mg/m^2 to about 50 mg/m^2;
- the effective antineoplastic amount of mitoantrone is from about 10mg/m^2 to about 20 mg/m^2;
- the effective antineoplastic amount of paclitaxel is from about 100 mg/m^2 to about 300 mg/m^2;
- the effective antineoplastic amount of docetaxel is from about 50 mg/m^2 to about 100 mg/m^2;
- the effective antineoplastic amount of vinorelbine is from about 15 mg/m^2 to about 30 mg/m^2;
- the effective antineoplastic amount of cyclophosphamide is from about 100 mg/m^2 to about 1500 mg/m^2;
- the effective antineoplastic amount of melphalan is from about 1 mg/m^2 to about 10 mg/m^2;
- the effective antineoplastic amount of 5-fluorouracil is from about 100 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of capecitabine is from about 10 mg/m^2 to about 1000 mg/m^2;

- the effective antineoplastic amount of methotrexate is from about 10 mg/m^2 to about 1000 mg/m^2;
- the effective antineoplastic amount of topotecan is from about 1 mg/m^2 to about 5 mg/m^2;
- the effective antineoplastic amount of irinotecan is from about 50 mg/m^2 to about 350 mg/m^2;

and the effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.

18. A method according to claim 17, wherein the amount of aromatase inhibitor exemestane may vary from about 5 to about 50 mg, fadrozole from about 0.5 to about 10 mg, letrozole from about 0.5 to about 5 mg, and anastrozole from about 0.5 to about 5 mg.

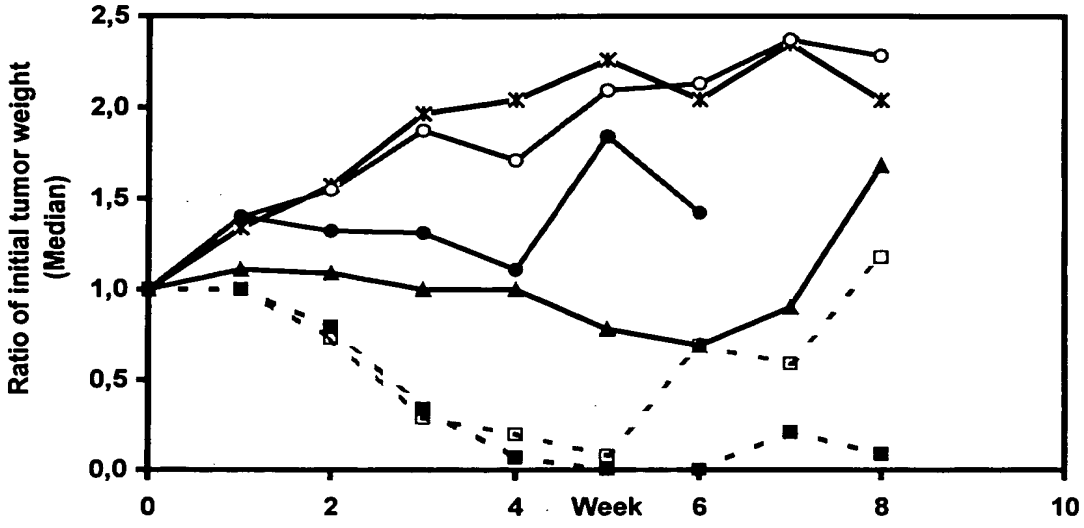
19. A method for lowering the side effects in humans caused by breast cancer therapy with an antineoplastic agent, the method comprising administering to a human in need thereof a combined preparation comprising (a) an antineoplastic agent and (b) an aromatase inhibitor, in a quantity to produce a superadditive antitumor effect.

ABSTRACT

COMBINED METHOD OF TREATMENT COMPRISING AN AROMATASE INHIBITOR AND A FURTHER BIOLOGICALLY ACTIVE COMPOUND

A composition for use in breast cancer therapy in humans comprising, in amounts effective to produce a superadditive antitumour effect, (a) an antineoplastic agent in a pharmaceutically acceptable carrier and/or diluent, and (b) an aromatase inhibitor in a pharmaceutically acceptable carrier and/or diluent.

Fig. 1


Ratio of initial tumor weight (Median)
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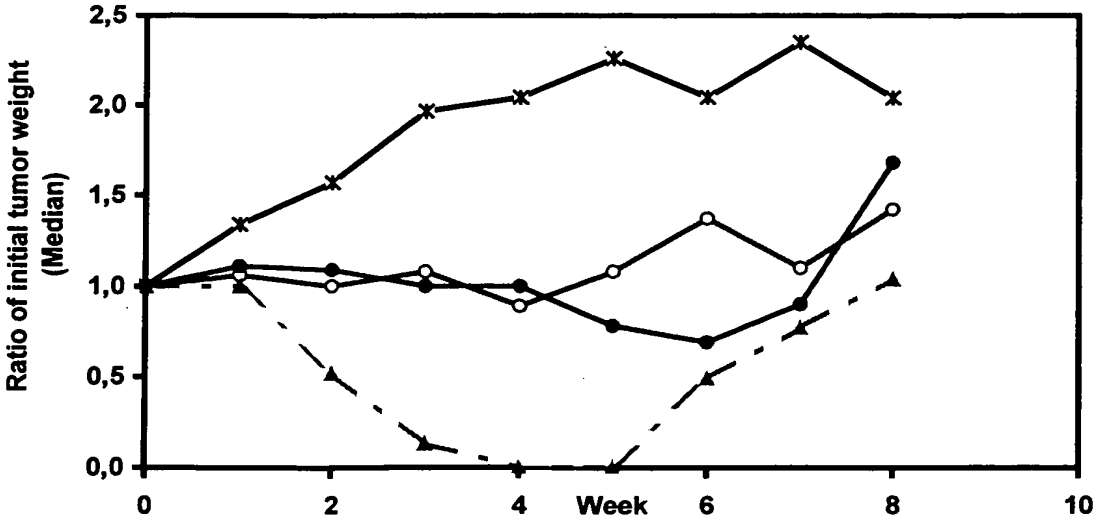
1,0
0,5
0,0
0
2
4
Week
6
8
10

Fig. 2


Ratio of initial tumor weight (Median)
2,5
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